

DESCRIPTION

PROCESS FOR PRODUCING A FLUORINE-CONTAINING COMPOUND

TECHNICAL FIELD

The present invention relates to a process for
5 effectively producing a fluorine-containing compound
having such a structure that two fluorine atoms are
bonded to one carbon atom ($-\text{CF}_2$), i.e. a geminal difluoro
structure. The fluorine-containing compound of the
formula (2) of the present invention is a compound useful
10 as e.g. perfume, pharmaceuticals, agricultural chemicals
and chemical agents.

BACKGROUND ART

As a method for introducing a fluorine atom bonded
to a carbon atom into a compound, (a) a method of acting
15 a fluorinating agent which generates fluorine anions
(such as KF or HF) on a chlorine atom bonded to a carbon
atom to carry out a nucleophilic substitution reaction of
 F^- . As a method for obtaining a fluorine-containing
compound having a geminal difluoro structure by means of
20 said method, a method of fluorinating a compound having a
geminal dichloro structure ($-\text{CCl}_2$ structure) at the
corresponding part as a material may be mentioned.

However, it is generally difficult to selectively
obtain a desired compound having a geminal dichloro
25 structure to be used for the reaction of (a), and such a
method can hardly be employed as an industrial production
method, such being problematic. Particularly, when a

ketone part of a compound having a C-H structure at the α -position of a ketone is converted to a geminal dichloro structure, a reaction such as elimination of HCl takes place, whereby at least two types of compounds are formed, and it tends to be difficult to obtain an intended compound with a high yield, such being problematic. Accordingly, a method of converting a ketone to a geminal dichloro structure, followed by fluorination, has not been carried out.

Further, as another method of synthesizing a fluorine-containing compound having a geminal difluoro structure by another method, (b) a method of reacting a carbonyl compound or a thiocarbonyl compound with a fluorinated sulfur type fluorinating agent (hereinafter referred to as SF compound) such as SF₄ (J. Ing. Nucl. Chem., 1964, 26, 41.) or diethylaminosulfur trifluoride ((CH₃CH₂)₂NSF₃; hereinafter referred to as DAST) (Tetrahedron Lett., 1991, 32, 5963.) has been known. Further, in recent years, a method of employing DAST wherein a substituent on a nitrogen atom is converted (U.S.P. 6,080,886) has been reported.

However, the SF compound in the method (b) is a compound which requires careful handling, and such a problem that a severe reaction which is difficult to control may occur in the after-treatment has been reported, and application as an industrial production method is difficult, such being problematic. Further, in

a case where a reaction is carried out by using the SF compound, removal of HF of the product may take place, whereby a fluoroolefin forms as a by-product, thus decreasing purity of the product. Further, depending upon the substrate used for the reaction, the difference in the boiling point between the fluoroolefin as the by-product and the intended compound is small, whereby a complicated separation operation may be required, or the yield may significantly decrease by the purification operation, such being problematic.

Further, a means to fluorinate a chloroolefin obtained by (c) Diels-Alder reaction with HF has been reported (USP 4,792,618). However, compounds to which the method (c) can be applied are limited in structure. Further, in many cases, isomers which are difficult to be separated and purified form as by-products, such being disadvantageous as a method for obtaining a geminal difluoro compound with a high purity.

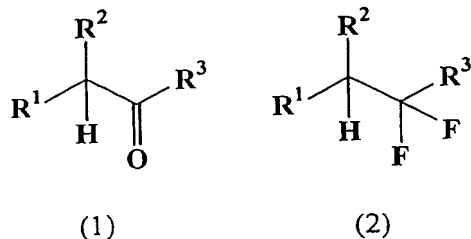
It is an object of the present invention to overcome the above problems, and to provide a process for synthesizing an intended compound having a geminal difluoro structure with a high yield from a carbonyl compound which is readily available.

DISCLOSURE OF THE INVENTION

The present inventors have conducted extensive studies to overcome the above problems and as a result, they have found a process for producing a geminal

difluoro product with a high purity from a carbonyl compound by carrying out a reaction comprising two steps.

Namely, the present invention provides a process for producing a fluorine-containing compound of the following formula (2), which comprises reacting a compound of the following formula (1) with a compound of the formula X-Z or a compound of the formula Z_2O (wherein Z is a monovalent group which gives a leaving group of the structure -OZ, and X is a chlorine atom, a bromine atom or an iodine atom), and then acting a fluorinating agent which generates fluorine anions thereon to obtain the fluorine-containing compound of the following formula (2):



wherein each of R^1 , R^2 and R^3 which are independent of one another, is a hydrogen atom, a fluorine atom or a monovalent organic group, or two selected from R^1 , R^2 and R^3 together form a bivalent organic group, and the other one is a hydrogen atom, a fluorine atom or a monovalent organic group.

In the present specification, the compound of the formula (1) will be referred to as a compound (1). The same applies to compounds of other formulae. Further,

the pressure in the present specification is represented by an absolute pressure.

In the present specification, a halogen atom is a fluorine atom, a chlorine atom, a bromine atom or an iodine atom. An organic group is a group which essentially has a carbon atom. A monovalent group is a group having one binding site, and it may be a monovalent organic group or a monovalent atom. A bivalent group is a group having two binding sites, and it may be a bivalent organic group or a bivalent atom.

In a case where each of R^1 , R^2 and R^3 is a monovalent organic group, each of these groups is selected from monovalent groups which do not change by the reaction of the present invention, and preferred is a group selected from a monovalent aliphatic saturated hydrocarbon group, a monovalent aliphatic saturated hydrocarbon group substituted with a monovalent aromatic hydrocarbon group and/or a monovalent heterocyclic group, a monovalent aromatic hydrocarbon group and a monovalent heterocyclic group, a group having an ethereal oxygen atom, a thioethereal sulfur atom or a substituted nitrogen atom inserted between a carbon-carbon bond of said selected group, and an ethereal oxygen atom, a thioethereal sulfur atom or a substituted nitrogen atom bonded to the binding terminal of said selected group.

Further, at least one hydrogen atom in each of the monovalent aromatic hydrocarbon group, the monovalent

aliphatic hydrocarbon group substituted with a monovalent aromatic hydrocarbon group and/or a monovalent heterocyclic group, and the monovalent heterocyclic group may be substituted with a substituent.

5 The substituent is preferably an alkyl group, a cycloalkyl group or the monovalent aromatic hydrocarbon group. Further, in addition to the above, preferred as the substituent is a group selected from a fluorine atom, an alkoxyl group, an alkyl-substituted amino group, a
10 cycloalkyl-substituted amino group, an aryloxy group, an aryl-substituted amino group, $-\text{NO}_2$, $-\text{CN}$, $-\text{COOR}^a$, $-\text{CONR}^b\text{R}^c$, $-\text{SO}_2\text{NR}^b\text{R}^c$, $-\text{S}(\text{O})\text{R}^a$, $-\text{S}(\text{O})_2\text{R}^a$ and $-\text{C}(\text{OR}^a)_3$ (hereinafter said groups to be selected are referred to as substituent (r)).

15 Here, each of R^a , R^b and R^c which are independent of each other, is a C_{1-20} alkyl group (such as a methyl group, an ethyl group, a 2-propyl group or a tert-butyl group), a C_{3-8} cycloalkyl group (such as a cyclopropyl group, a cyclopentyl group or a cyclohexyl group), an
20 alkyl group substituted with at least one aryl group (such as a benzyl group, a phenethyl group or a trityl group), an alkyl group substituted with at least one monovalent heterocyclic group (such as a 2-pyridylmethyl group), an aryl group (such as a phenyl group); a
25 substituted aryl group (such as a 3-chlorophenyl group, a 4-methylphenyl group, a 2,3-dimethoxyphenyl group, a 2-nitrophenyl group or a 4-aminophenyl group) or a

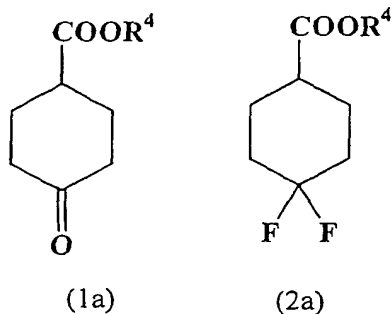
fluoroalkyl group (such as $-\text{CF}_3$, $-\text{CF}_2\text{CF}_3$, $-\text{CH}_2\text{CF}_3$).

In a case where each of R^1 , R^2 and R^3 is a monovalent organic group, preferred is an alkyl group, a cycloalkyl group, a phenyl group, an alkyl-substituted phenyl group, an alkyl-substituted monovalent heterocyclic group, a benzyl group or a group having at least one hydrogen atom in said group substituted with the above substituent (r).

Further, in a case where two selected from R^1 , R^2 and R^3 together form a bivalent organic group (in this case, the other one group is a hydrogen atom, a fluorine atom or a monovalent organic group), preferred is a bivalent organic group selected from a bivalent saturated hydrocarbon group, a bivalent saturated hydrocarbon group containing an ethereal oxygen atom ($-\text{O}-$), a bivalent saturated hydrocarbon group containing a thioethereal sulfur atom ($-\text{S}-$) and a bivalent saturated hydrocarbon group containing $-\text{NH}-$, and a group having at least one hydrogen atom bonded to a carbon atom in said bivalent organic group substituted with the above substituent (r). As the bivalent saturated hydrocarbon group, an alkylene group is preferred, and a $-(\text{CH}_2)_n-$ (wherein n is an integer of at least 1) is preferred.

As the compound (1) of the present invention, preferred is a compound wherein R^1 is a hydrogen atom, and R^2 and R^3 together form a tetramethylene group substituted with $-\text{COOR}^4$, particularly preferred is a compound (1a) wherein R^1 is a hydrogen atom, and R^2 and R^3

together form $-\text{CH}_2\text{CH}(\text{COOR}^4)\text{CH}_2\text{CH}_2-$. Further, as the
 fluorine-containing compound (2) as an intended compound
 of the present invention, preferred is the following
 fluorine-containing compound (2a) corresponding to the
 5 compound (1a). Further, as intermediates (3) to (7) as
 described hereinafter, preferred are compounds wherein R^1
 is a hydrogen atom, and R^2 and R^3 together form a
 tetramethylene group substituted with $-\text{COOR}^4$
 (particularly a group $-\text{CH}_2\text{CH}(\text{COOR}^4)\text{CH}_2\text{CH}_2-$).



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wherein R^4 is a group similar to the above R^a , it is a
 C_{1-20} alkyl group, a C_{3-8} cycloalkyl group, an alkyl group
 substituted with at least one aryl group, an alkyl group
 substituted with at least one monovalent heterocyclic
 15 group, an aryl group, a substituted aryl group or a C_{1-20}
 fluoroalkyl group, preferably a methyl group, an ethyl
 group, a phenyl group, a benzyl group, a propyl group, an
 isopropyl group, a butyl group, a tert-butyl group, a
 hexyl group, a cyclohexyl group or a substituted phenyl
 20 group, particularly preferably a C_{1-20} alkyl group or a
 C_{3-8} cycloalkyl group. A compound (1a) wherein R^4 is
 methyl or ethyl is a known compound, and is a compound

available as a commercially available product or by a known production method. Another compound (1a) can be derived from the known compound.

In the present invention, first, the compound (1) is
 5 reacted with a compound of the formula X-Z (hereinafter referred to as compound A) or a compound of the formula Z_2O (hereinafter referred to as compound B).

Z in the compound A is a monovalent group which gives a leaving group of the structure -OZ. -OZ is a
 10 leaving group which leaves and is substituted with a fluorine atom in a reaction with a fluorinating agent of the present invention. Z may, for example, be a hydrogen atom (-OH is a leaving group), $-POCl_2$ ($-OP(O)Cl_2$ is a leaving group) or a $-COCH_3$ ($-OCOCH_3$ is a leaving group).
 15 X in the compound A (X-Z) is a chlorine atom, a bromine atom or an iodine atom. X is substituted with a fluorine atom in the reaction with a fluorinating agent. X in the compound A is preferably a chlorine atom.

The compound A is preferably a compound represented
 20 by HX , POX_3 , PX_5 , SOX_2 , SO_2X_2 , $(COX)_2$, R^5COX , R^5SO_2X or $(R^5O)_3P(O)X$. R^5 is a monovalent organic group, and preferably a group selected from an alkyl group, a halogenated alkyl group, an aryl group, an alkyl-substituted aryl group, an aryl-substituted alkyl group
 25 or an (alkyl-substituted aryl)alkyl group.

Among them, more preferred as the compound A is a compound represented by POX_3 , PX_5 , SOX_2 , $(COX)_2$, CH_3COCl ,

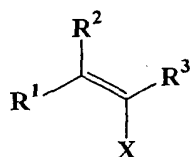
PhCOCl (wherein Ph is a phenyl group, the same applies hereinafter), $\text{CH}_3\text{CH}_2\text{COCl}$, $p\text{-CH}_3\text{C}_6\text{H}_4\text{SO}_2\text{Cl}$ (wherein C_6H_4 is a phenylene group), $\text{CH}_3\text{SO}_2\text{Cl}$, $\text{CF}_3\text{SO}_2\text{Cl}$, $(\text{PhO})_2\text{PO-X}$, $(\text{CH}_3\text{CH}_2\text{O})_2\text{PO-X}$ or $(\text{CH}_3\text{O})_2\text{PO-X}$, and PX_5 is particularly preferred from such a reason that treatment after the reaction is readily carried out. These compounds A are readily available compounds.

Z in the compound B (Z_2O) may be a group similar to Z in the compound A. As the compound B, preferred is $(\text{R}^5\text{CO})_2\text{O}$ or $(\text{R}^5\text{SO}_2)_2\text{O}$ (wherein R^5 is as defined above), particularly preferred is $(\text{CH}_3\text{CO})_2\text{O}$, $(\text{PhCO})_2\text{O}$ or $(\text{CF}_3\text{SO}_2)_2\text{O}$.

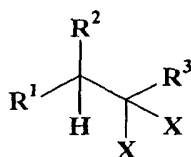
In the present invention, the compound (1) is reacted with the compound A or the compound B (hereinafter this reaction step will be referred to as a first step). The product in the first step reaction (hereinafter referred to as an intermediate) varies depending upon e.g. the structure of the compound (1) used for the reaction, the structure of the compound A or the compound B and reaction conditions. In the present invention, such an intermediate may be isolated as the case requires, but the intermediate is introduced to an intended fluorine-containing compound (2) even when a fluorination reaction in the subsequent second step is carried out without isolating the intermediate.

In a usual case, in the reaction of the compound (1) with the compound A, at least one type of a compound

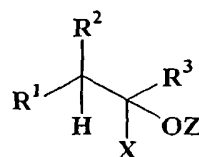
selected from compounds (3) to (7) may form as an intermediate. R^1 , R^2 , R^3 , X and Z in the following formulae (3) to (7) correspond to the compound A used for the reaction. In the present invention, the second step may be carried out after the formed intermediate is taken out, or the second step may be carried out without taking such a compound out. Said intermediate may be one type or at least two types, and at least two types are formed in a usual case.



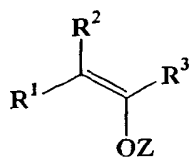
(3)



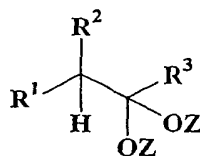
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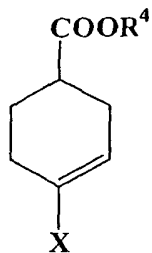
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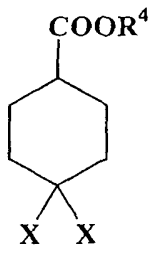
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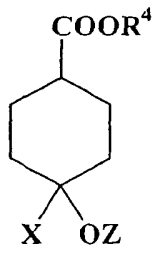
As compounds (3) to (7), compounds (3a) to (7a), respectively, are preferred. X, Z and R^4 in the following formulae are as defined above, and preferred embodiments are also as described above.



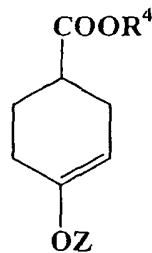
(3a)



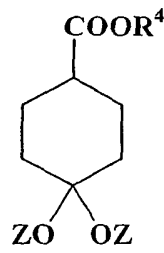
(4a)



(5a)



(6a)



(7a)

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On the other hand, in the reaction of the compound (1) with the compound B, usually a compound (6) and/or a compound (7) forms as an intermediate. R^1 , R^2 , R^3 and Z in the following formulae (6) and (7) correspond to the compound B used for the reaction. In the present invention, the formed intermediate may be taken out and then introduced to the second step, or the fluorination reaction may be carried out without taking such a compound out. The intermediate may be one type or two types, and in a usual case, at least two types of compounds are preferably formed.

The intermediate when the compound (1a) is reacted with the compound B, preferred is at least one type of a compound selected from the compound (6a) and the compound (7a), and usually the compound (6a) and the compound (7a) are preferred. Z and R^4 in the formulae are as defined above, and the preferred embodiments are as described above.

The above compounds (3) to (7), particularly the compounds (3a) to (7a) are compounds having boiling points close to one another, and they are respectively unstable compounds, and accordingly it tends to be difficult to separate them by a conventional separation and purification operation. However, according to the process of the present invention, even if at least two types of intermediates are formed, they do not have to be taken out, and can be directly used to the subsequent

second step.

It is not necessary to isolate the formed intermediates, but it is preferred to carry out an after-treatment which is carried out after a usual reaction.

5 As a method of the after-treatment, distillation of the reaction solvent, extraction with a solvent, washing with an acid or alkali aqueous solution and/or water, crystallization or column chromatography purification may, for example, be mentioned.

10 The amounts of the compound A and the compound B used for the reaction are usually preferably from 0.1 to 100 times the molar quantity of the compound (1), particularly preferably from 1.0 to 10 times the molar quantity. The reaction temperature is usually preferably
15 from -50 to 250°C in view of e.g. handling efficiency, particularly preferably within a range of from -20 to 200°C. The reaction time is usually preferably from 0.1 to 72 hours, particularly preferably from 0.5 to 48 hours. The reaction pressure is optionally changed
20 depending upon the reaction temperature, and the reaction is carried out preferably by a liquid phase reaction, and thus it is preferably from 0.01 MPa to 10.00 MPa, more preferably from 0.08 MPa to 3.00 MPa.

The first step reaction may be carried out in the
25 presence of a solvent. As the solvent, one type or at least two types of solvents inert in the reaction may be employed. As the solvent, a hydrocarbon type solvent

such as toluene, xylene, benzene, cyclohexane or n-hexane, a halogenated hydrocarbon type solvent such as dichloromethane, dichloroethane, carbon tetrachloride, chloroform, chlorobenzene or 1,2-dichlorobenzene, an ester type solvent such as ethyl acetate or n-butyl acetate, an ether type solvent such as diethyl ether, diisopropyl ether, methyl tert-butyl ether, ethylene glycol dimethyl ether, tetrahydrofuran or dioxane, a nitrile type solvent such as acetonitrile, an amide type solvent such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone or N-methylpyrrolidinone, or dimethylsulfoxide, phosphorus oxychloride or water may, for example, be mentioned.

As the solvent, preferred are e.g. ethyl acetate, acetonitrile, dichloromethane, chloroform, chlorobenzene, 1,2-dichlorobenzene, methyl tert-butyl ether, dimethylsulfoxide, dimethylformamide, phosphorus oxychloride, hexane, toluene or xylene. When a solvent is used, its amount is preferably from 0.5 to 200 mL per 1 g of the compound (1) from such a reason as readiness in the after-treatment, particularly preferably from 1 to 50 mL.

The first step reaction may be carried out in the presence of a base. The base may be an organic base or an inorganic base. The organic base may, for example, be triethylamine, diisopropylethylamine, pyridine, 4-dimethylaminopyridine, morpholine, 1,5-

diazabicyclo[4.3.0]nona-5-ene, 1,8-
diazabicyclo[5.4.0]undeca-7-ene, sodium methoxide or
potassium tert-butoxide. The inorganic base may, for
example, be an alkali metal hydroxide such as sodium
5 hydroxide, potassium hydroxide or lithium hydroxide, an
alkaline earth metal hydroxide such as calcium hydroxide
or magnesium hydroxide, an alkali metal carbonate such as
sodium carbonate or potassium carbonate, an alkali metal
hydrogencarbonate such as sodium hydrogencarbonate or
10 potassium hydrogencarbonate, or an alkali metal hydride
such as sodium hydride.

In a case where a base is employed, its amount is
usually preferably from 0.1 mol to 200 mol per 1 mol of
the compound (1), particularly preferably from 0.2 mol to
15 100 mol.

Then, in the present invention, a reaction with a
fluorinating agent (hereinafter this reaction step will
be referred to as the second step) is carried out. In
the second step, even if at least two types of the
20 intermediates are formed in the first step, they are used
without being separated. Further, in a case where at
least two types of products are formed in the first step,
their proportion and the like are not particularly
limited and they may be used for the second step.

25 The second step is a reaction with a fluorinating
agent, and the fluorinating agent in the present
invention causes a fluorination reaction by the action of

fluorine anions. The fluorinating agent which generates fluorine anions in the second step may, for example, be HF, pyridinium polyhydrogen fluoride, tetrabutylammonium dihydrogen trifluoride, tetrabutylammonium fluoride, 5 AgF₂, SbF₅, SbF₃, SbF₃Cl₂, CrF₃, HgF, HgF₂, RbF, KF, NaF, LiF, KSO₂F, KHF₂, ZnF₂, CaF₂, CsF, Na₂SiF₆, AsF₃, BrF₃, IF₅, IF₇, NbF₅ or TaF₅. Among them, preferred is HF or KF since they are available at a low cost, and the after-treatment is readily carried out with them, and HF is 10 particularly preferred.

The amount of the fluorinating agent is usually preferably from 0.1 to 100 times the molar quantity of the total number of mols of the product in the first step, particularly preferably from 0.2 to 50 times the 15 molar quantity, with respect to the fluorinating agent other than HF. In the case of HF, its amount is preferably from 0.1 to 500 times by mass the total mass of the product in the first step, particularly preferably from 0.5 to 100 times by mass.

20 The reaction temperature in the second step is usually preferably from -50 to 250°C in view of e.g. operation efficiency, particularly preferably from -20 to 200°C. The reaction temperature is not necessarily constant, and is preferably optionally adjusted depending 25 upon the progress of the reaction. The reaction time in the second step is usually preferably from 0.1 to 72 hours, particularly preferably from 0.5 to 48 hours. The

reaction pressure is optionally changed depending upon the reaction temperature, and it is preferably from 0.01 MPa to 10.0 MPa, particularly preferably from 0.08 MPa to 3.00 MPa, especially preferably the pressure in the vicinity of normal pressure, from such a reason that the reaction can be carried out as a liquid phase reaction. Further, in a case where hydrogen chloride is generated in the reaction, the reaction system is preferably at least 0.01 MPa, particularly preferably from 0.1 MPa to 0.5 MPa, from such a reason that hydrogen chloride is occasionally removed, whereby the fluorination reaction is accelerated. The second step reaction is carried out preferably by using a reaction vessel made of hastelloy or a reaction vessel having the inner surface lined with a fluororesin.

The second step reaction may be carried out in the presence of a catalyst. The catalyst is preferably a Lewis acid catalyst. As the Lewis acid catalyst, the following compounds may be mentioned. The halogen atom in the following metal halides may be one type or at least two types, and is preferably a bromine atom, a chlorine atom or an iodine atom.

The Lewis acid catalyst may, for example, be an alkali metal halide, an alkaline earth metal halide, a transition metal halide, silane halide, germanium halide, boron halide, aluminum halide, gallium halide, indium halide, thallium halide, tin halide, titanium halide,

lead halide, bismuth halide, antimony halide, tellurium
halide, selenium halide, germanium halide, niobium
halide, IF_3 , BF_3 or a metal oxide, and preferred are
antimony(III) halide, antimony(V) halide, aluminum(III)
5 halide, chromium(III) halide, silver(I) halide,
mercury(I) halide, mercury(II) halide, calcium(II)
halide, boron(III) halide, arsenic(III) halide,
magnesium(II) halide, beryllium(II) halide, niobium(V)
halide, thallium(V) halide, rubidium(III) halide, tin(IV)
10 halide, titanium(IV) halide, aluminum oxide and vanadium
oxide. Among them, e.g. SbF_5 , SbCl_5 , SbCl_2F_3 , NbCl_5 ,
 NbClF_4 , NbF_5 , TaF_5 , TaCl_5 and TaClF_4 may be mentioned as
preferred examples, since their reactivity is high.

The amount of the Lewis acid catalyst is usually
15 preferably from 0.1 to 100 mol% based on the compound
(1), particularly preferably from 0.2 to 50 mol%.
Further, the catalyst may be added after the fluorinating
agent and the product in the first step are mixed, or the
catalyst may be added to the fluorinating agent, and then
20 the product in the first step is added thereto.

The second step reaction may be carried out in the
presence of a solvent. The solvent may optionally be
selected from solvents inert in the fluorination
reaction. One type or at least two types of the solvents
25 may be used.

The solvent may, for example, be a hydrocarbon type
solvent such as toluene, xylene, benzene, cyclohexane or

n-hexane, a chlorofluorocarbon type solvent or a fluorocarbon type solvent such as HFC-134a, HCFC-22, HCFC-124, HFC-125, HFC-32, HFC-134, HCFC-123, HCFC-124 or HCFC-225, an ether type solvent such as diethyl ether, 5 diisopropyl ether, methyl tert-butyl ether, ethylene glycol dimethyl ether, tetrahydrofuran or dioxane, an ester type solvent such as ethyl acetate or n-butyl acetate, a cyano type solvent such as acetonitrile, an amide type solvent such as N,N-dimethylformamide, N,N- 10 dimethylacetamide, N-methylpyrrolidone or N-methylpyrrolidinone, a halogenated aromatic hydrocarbon type solvent such as dichlorobenzene or chlorobenzene, or dimethylsulfoxide or water.

Among them, as the solvent in the second step, 15 preferred is e.g. ethyl acetate, acetonitrile, dimethylsulfoxide, dimethylformamide, hexane, toluene, xylene, dioxane or HCFC-225. Further, in a case where a solvent is used, its amount is preferably from 0.1 to 200 mL per 1 g of the product in the first step, in view of 20 e.g. the after-treatment, particularly preferably from 1 to 50 mL.

In the production process of the present invention, a fluorine-containing compound (2) having a geminal difluoro structure is obtained. R^1 , R^2 and R^3 in the 25 fluorine-containing compound (2) correspond to those in the compound (1) and are as defined above. The reaction crude product containing the formed fluorine-containing

compound (2) is preferably subjected to an after-treatment depending upon the purpose. As a method of the after-treatment, a method of the after-treatment similar to that in the case of the first step may be mentioned, and distillation is preferred. Particularly when HF is used as a fluorinating agent, it is preferred to vaporize and remove excess HF as far as possible, followed by neutralization to remove HF, and to carry out the after-treatment.

10 The fluorine-containing compound (2) obtained by the production process of the present invention is a compound useful as perfume, pharmaceuticals, agricultural chemicals and chemical agents, or as intermediates therefor. Particularly, the fluorine-containing compound 15 (2a) is a compound useful as an intermediate for pharmaceuticals and agricultural chemicals.

BEST MODE FOR CARRYING OUT THE INVENTION

Now, the present invention will be explained with reference to Examples, but the present invention is not 20 limited thereto.

EXAMPLE 1

Example for first step reaction

Phosphorus pentachloride (136 g, 0.65 mol) and 325 mL of toluene were mixed in an atmosphere of nitrogen, and while keeping the temperature to be within a range of 25 from 0 to 10°C by cooling with ice water, ethyl 4-oxocyclohexanecarboxylate (111 g, 0.65 mol) was dropwise

added thereto over a period of 30 minutes. The solid part gradually dissolved from the initial suspended state, and the suspension became a completely clear solution in the middle of the dropwise addition. After completion of the dropwise addition, stirring was continued for 10 minutes, and disappearance of the material was confirmed by gas chromatography. A distillation apparatus was attached to a reaction flask, and at least half the content (369 g) was distilled off under reduced pressure. 190 g of an oily substance remaining in the flask was diluted with toluene, washed with 200 mL of water, 50 mL of an aqueous sodium chloride solution and 50 mL of water, and dried over magnesium sulfate and concentrated by an evaporator, and further dried under reduced pressure in vacuum to obtain 146 g of a redish brown oily substance. The redish brown oily substance contained ethyl 4-chloro-3-cyclohexenecarboxylate, ethyl 4,4-dichlorocyclohexanecarboxylate and toluene in amounts of 52%, 28% and 20%, respectively.

EXAMPLE 2

Example for second step reaction

Anhydrous hydrogen fluoride (60 g, 3 mol) was introduced to a 200 mL hastelloy autoclave under reduced pressure, and antimony pentachloride (3 g, 0.01 mol) was added thereto under nitrogen pressure of 0.5 MPa, followed by stirring at room temperature for 1 hour (234

rpm). During this stirring, the internal pressure increased from 0.15 MPa to 0.17 MPa. In such a state, the above chlorinated product (18.8 g, 75.2 mmol) was added thereto dividedly in three times under a nitrogen pressure of 0.6 MPa, whereupon the internal pressure became 0.3 MPa, and the internal temperature increased from 14°C to 21°C. Stirring was carried out at room temperature for 1 hour, whereupon the internal temperature decreased to 16°C, and the internal pressure increased to 0.32 MPa. The autoclave was heated over a period of 30 minutes until the internal temperature become 50°C, and heating was carried out for 1 hour. A needle valve was opened when the internal pressure became 0.4 MPa to decrease the internal pressure to 0.3 MPa, and this operation was repeatedly carried out totally 6 times. After no increase in the internal pressure was observed, the autoclave was heated to 50°C to eject excess hydrogen fluoride, and the autoclave was opened, and the content was added to a potassium hydrogencarbonate aqueous solution cooled with ice. After extraction with ethyl acetate, the organic layer was washed with water, dried over magnesium sulfate and concentrated by an evaporator to obtain 15.13 g of blackish brown oily substance. The oily substance was distilled off under reduced pressure to obtain ethyl 4,4-difluorocyclohexanecarboxylate (2 g, purity of at least 99% as calculated from peak area by gas chromatography).

^1H -NMR δ (ppm): 1.26 (3H, t), 1.7 to 2.5 (9H, m),
4.14 (2H, q).

^{19}F -NMR δ (ppm): -94.9 (d), -100.1 (d).

INDUSTRIAL APPLICABILITY

5 According to the production process of the present
invention, a fluorine-containing compound having a
geminal difluoro structure can be produced efficiently
and position-selectively, employing a carbonyl compound
which is readily available as a material by a two-step
10 reaction. In the process of the present invention, even
if at least two types of intermediates are formed in the
first step, it is possible to carry out the subsequent
step without separating them, and a fluorine-containing
compound with a high purity can be obtained from the
15 product in the second step. Accordingly, a fluorine-
containing compound with a high purity can be obtained
without carrying out a complicated separation operation
in the process of the production steps or on the product.
Further, the fluorination reaction may be carried out by
20 using e.g. HF, such being advantageous since the
production cost can be decreased as compared with a
conventional method, and this process can be an
industrially useful production process.

 The entire disclosure of Japanese Patent Application
25 No. 2001-024174 filed on January 31, 2001 including
specification, claims and summary is incorporated herein
by reference in its entirety.